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Rituximab and Cytokine Release Syndrome

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Key Words

Rituximab · Cytokine release syndrome · Systemic inflammatory response syndrome · Mortality · Fatality · Lactic acidosis · Post-transplant lymphoproliferative disorder

Abstract

Rituximab is a biologic agent that is usually well tolerated. With its increasing use for a myriad of rheumatologic and immunologic conditions, post-marketing surveillance has revealed more side effects. Systemic inflammatory response syndrome associated with cytokine release syndrome (CRS) is a very rare entity associated with the use of rituximab and carries a very high morbidity and case fatality rate. Cases of CRS reported within the literature are of patients with a very high tumor burden leading to a catastrophic cascade of events. We report the case of a patient having post-transplant lymphoproliferative disorder who died of fatal lactic acidosis and CRS within 24 h of receiving rituximab. Understanding the pathophysiology of such cases and identifying patients at risk may help to possibly avert this life-threatening complication.

Case Presentation

A 72-year-old Caucasian man with a past medical history notable for orthotopic heart transplantation for non-ischemic cardiomyopathy, Type 2 diabetes mellitus, chronic renal insufficiency, idiopathic thrombocytopenic purpura, and cryptogenic cirrhosis was initially admitted to the Intensive Care Unit for refractory acute kidney injury in the setting of newly diagnosed post-transplant lymphoproliferative disorder (PTLD).

He initially went to a local hospital for abdominal pain where his blood work revealed acute kidney injury superimposed on his chronic renal insufficiency. Imaging showed unilateral hydronephrosis and a renal stone at the ureterovesical junction. Hence, he had a ureteral stent placed. However, his renal function did not improve.

During the same admission, the patient was found to have several subcutaneous violet nodules over the abdomen (fig. 1). Biopsy of these lesions showed diffuse large B-cell lymphoma, after which he was transferred to a tertiary care center for further management and care.

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Further evaluation showed CD20+ cells on bone marrow biopsy. A computerized tomography scan of his chest, abdomen and pelvis showed evidence of new extensive omental, peritoneal and mesenteric lymph node involvement and pulmonary nodules depicting severe PTLD. He was initially started on high-dose prednisone for lymphoma, which was attributed to PTLD.

Given worsening of his renal function in the setting of hypotension and anasarca, the patient was started on continuous veno-venous hemodialysis in the Intensive Care Unit. He was also empirically started on treatment with broad-spectrum antibiotics and anti-fungals, and was pressor-dependent. Infectious workup was negative, and a diagnostic paracentesis revealed lymphocytic predominant exudate but negative Gram stain and cultures. The patient remained stable on continuous veno-venous hemodialysis with a stable pressor requirement for several days.

Given the CD20 positivity on the bone marrow biopsy and a Ki-67 of more than 90% (representing the aggressive nature of the PTLD) the patient was started on rituximab. He tolerated the infusion without any immediate complications. However, within 18 h of the first rituximab infusion, he developed severe worsening abdominal pain, profound refractory lactic acidosis, increasing pressor requirements and respiratory failure requiring emergent intubation. He also had multiple episodes of bradycardic arrests due to metabolic derangements. Labs eventually revealed disseminated intravascular coagulation. The patient eventually developed hemoptysis and bronchoscopy revealed blood but no clots. Hypotension became refractory to pressors and the patient eventually died of asystole. During his worsening clinical condition, there was no electrical or biochemical evidence of a myocardial infarction. Imaging studies also failed to demonstrate any bowel perforation. There was no evidence of active tumor lysis demonstrated by stable lactate dehydrogenase and uric acid levels. The patient's death was attributed to severe systemic inflammatory response syndrome (SIRS) versus cytokine release syndrome (CRS) leading to shock and lactic acidosis.

Severe lactic acidosis may be related to the effects of the rapid destruction of tumor cells by rituximab (but not as an effect of the drug itself) leading to cytokine release from these cells, causing hypoperfusion, hypotension and shock. Unfortunately, the therapy is supportive and carries a high morbidity and mortality.

In the following, we will provide a discussion on along with a review of cases of CRS associated with the use of rituximab.

Discussion

Rituximab is a monoclonal antibody against the B-cell marker CD20 and is used in a variety of conditions including lymphoproliferative disorders and autoimmune diseases [1–3]. Rituximab is usually well tolerated. However, with its increasing prolonged as well as widespread use for multiple conditions including refractory idiopathic thrombocytopenic purpura, refractory thrombotic thrombocytopenic purpura, and post-traumatic lymphoproliferative disorder among others, post-marketing surveillance has resulted in increasing identification of rare side effects [4, 5].

The side effects of rituximab are reported based on the grading system for reporting adverse effects from chemotherapy (CTCAE: Common Terminology Criteria for Adverse Events Version 4.0); Grade 3 and 4 represent moderate to severe adverse events and Grade 5 represents fatalities [6].

Based on side effects reported from multiple randomized control trials using rituximab, the most side effects are of Grade 1 or 2 severity; Grade 3 and 4 are not as common, while mortality resulting directly or indirectly after administration of the drug is extremely rare [7–9]. A post-marketing surveillance database on rituximab indicates a mortality of 0.04–0.07% associated with the drug [10].

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Severe SIRS and disseminated intravascular coagulation occurring within 24 h of administering rituximab have rarely been reported in the literature (**table 1**). The pathophysiology of this reaction is attributed to release of cytokines generally after the first administration of rituximab. If uncontrolled, this can lead to SIRS.

'The underlying mechanism of cytokine-release syndrome (CRS) is related to changes of serum cytokine levels due to rapid injection of the antibody. CRS is characterized by an increase of inflammatory cytokines such as IFN-γ, IL-8 and TNF-α occurring about 90 min after the first infusion. In severe cases of CRS after *rituximab*, a 5 to 10-fold increase in liver enzymes, elevation of D-dimer, lactate dehydrogenase and prolongation of protrombin time are also commonly observed' [10].

According to one of the earlier reports on CRS with rituximab, the author noted that 'subsequent communication with the manufacturer (Roche Pharmaceuticals, Nutley, N.J., USA) revealed that there had been 8 other fatalities possibly related to rituximab-induced cytokine release syndrome' [11].

Similarly, in a series of 9 patients with B-cell chronic lymphocytic leukemia, Winkler et al. [12] noted a peak rise in serum levels of tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) in all of their patients. These changes in cytokine levels corroborated with clinical symptoms, including fever, chills, nausea, vomiting, hypotension, and dyspnea. Patients with lymphocyte counts exceeding 50.0×10^9/l experienced a severe CRS which was noted to be statistically significant.

One hypothesis for early release of cytokines is the agglutination of small lymphocytes in the lung, liver and spleen (leukostasis) which has been documented in autopsies [12]. Leukostasis in pulmonary vasculature may have contributed to hypoxia and respiratory compromise as noted in our patient. Alternatively, cytokine release from the apoptotic CD20+ tumor cells and a higher tumor burden in such patients may be making them more prone to CRS progressing to SIRS [13]. The rapid turnover of tumor cells in such cases may add markedly to the cytokine milieu leading to a catastrophic cascade of events [14].

CRS, though rare, is associated with considerable mortality. It would be very important clinically to identify which subsets of patients are more prone to developing the complication. Of note, many of these cases are not reported, nor are the presenting features classical [1]. Creating a registry may help in further advancement in terms of understanding the pathophysiology and possibly averting the complication.

Although this is based on case reports and causality is not established, it seems that fatal CRS/SIRS appear to occur in patients with a very high tumor burden, as noted in our patient as well. Caution needs to be exercised specifically in this subset of patients. For example, if patients develop similar but less severe reactions, a reduced dose and/or pre-treatment prior to rituximab infusions may be used to reduce the number and severity of reactions with subsequent doses [13]. Whether aggressive hydration or using anti-inflammatory agents such as steroids prior to administration of rituximab reduce the frequency and severity of side effects remains to be studied.

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Conclusions

Rituximab is a biologic agent that is usually well tolerated. With increasing, prolonged as well as widespread use for a myriad of conditions, including lymphoproliferative disorders and autoimmune conditions, side effects are now being reported more often. SIRS (from likely CRS) is a very rare entity associated with the use of rituximab and carries a very high morbidity and case fatality rate. Cases reported within the literature are of patients with apparently a very high tumor burden leading to a catastrophic cascade of events. Creating a registry may help in further advancement in terms of understanding the pathophysiology and possibly averting the life-threatening complication.

Acknowledgement

We are deeply indebted to the family of the patient for allowing us to present his information as a case report.

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Table 1. Case reports of severe CRS/SIRS

Study	Age/number of patients	Disease	Dose of rituximab	Serious adverse events/clinical course
Seifert et al. [10]	14 years	Pre-B acute lymphoblastic leukemia and anaplastic astrocytoma	375 mg/m^2	Initially had onset of severe back pain during the infusion, followed by SIRS 2 days later leading to mortality.
Lim et al. [11]	71 years	Stage I B-cell chronic lymphocytic leukemia	375 mg/m^2	Hypotension/hypoxemia leading to cardiovascular collapse 8 h after the first infusion of rituximab.
Winkler et al. [12]	9 patients	Chronic lymphocytic leukemia	375 mg/m^2	TNF-α and IL-6 peaked in all of their patients. Clinical symptoms included fever, chills, nausea, vomiting and hypotension. Rise was higher in patients with a higher lymphocyte count. No mortalities reported.
Byrd et al. [13]	73 years	Refractory transformed B-cell lymphoma presented with bulky lymphadenopathy	375 mg/m^2	Patient developed hypoxemia after the first infusion, followed by fever, tachycardia, rigors, and profuse diaphoresis. Decreased dose and pretreatment was done; no reaction noted in subsequent doses.
Byrd et al. [13]	5 patients	2 with chronic lymphocytic leukemia, 2 with prolymphocytic leukemia and 1 patient with diffuse large cell lymphoma	375 mg/m^2	Similar presentation as noted in Byrd et al. [13] above after the first infusion; associated with this was a rapid decline in the number of tumor cells. All patients had a high tumor burden.
Wu et al. [14]	3 patients	Intravascular large B-cell lymphoma	375 mg/m^2	Severe systemic reactions including dyspnea, hypoxia, tachycardia and hypotension within 24 h of their first dose of rituximab. Two required endotracheal intubation and mechanical ventilation support; one of the patients died.

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Fig. 1. Subcutaneous violet nodules noted over the abdomen of the patient. Biopsy of these lesions showed diffuse large B-cell lymphoma. Further evaluation showed CD20+ cells on bone marrow biopsy.

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Erratum

In the article 'Rituximab and Cytokine Release Syndrome' by Kulkarni et al. [Case Rep Oncol 2012;5:134–140] an error occurred. In the discussion section the third sentence must read: However, with its increasing prolonged as well as widespread use for multiple conditions including refractory idiopathic thrombocytopenic purpura, refractory thrombotic thrombocytopenic purpura, and post-**transplant** lymphoproliferative disorder among others, post-marketing surveillance has resulted in increasing identification of rare side effects [4, 5].

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